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ORIGINAL RESEARCH

Outcome of Treatment and Causes of Failure in Cancer Cervix Treated with Concurrent Chemoradiation

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ABSTRACT

Introduction: Cervix uteri cancer is most known disease found among women worldwide after breast, colorectal and lung cancers. The present study aimed to evaluate prognostic factors (patient, tumor and treatment) in carcinoma of cervix treated with concurrent chemoradiation.

Materials and Methods: A total of 40 patients included in the study and were planned to deliver by 3-Dimensional Conformal (DC) radiotherapy using four field box technique.Radiotherapy dose delivered to pelvic area was 50 Gy in 25 fractions at 200cGy/dayfollowed by intracavitary brachytherapy either 4 applications of 6 Gy/fraction or three applications of 7 Gy/fraction each as per departmental protocol. Chemotherapy dose delivered to patients received cisplatin 35mg/m2 weekly i.v. for a total of 5 cycles or 75mg/m2 triweekly i.v. for a total of 2 cycles. All patients were followed up at least 6 months from day of completion of treatment.

Result: Collected data was analyzed using Chi Square test to calculate level of significance it was found that significant prognostic factors are blood haemoglobin level (p = 0.006), stage (p = 0.016), histological grade (p = 0.039), lymph node involvement (p = 0.031), parametrial extension (p = 0.038), hydronephrosis (p = 0.015), tumor size (p = 0.038) and duration of treatment (p = 0.031) whereas age, histological type and subtype, total radiation dose and concurrent use of chemotherapy are found to be insignificant.

Conclusion: The outcomes of cancer cervix patent depends upon patient, tumor and treatment related factors. Presence of poor prognostic factors related to tumor may need intensification of the treatment by concurrent use of chemotherapy drugs, counteracting hypoxia by maintaining hemoglobin during treatment.

Keywords: Cancer cervix, Prognostic factors, Outcomes.

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INTRODUCTION

Cervical cancer is the second most common cancer in developing countries after carcinoma breast, but only the tenth most common in developed countries.[1] In India it is 16% of all cancers (ICMR).[2] More than 85% of the global burden occurs in the developing countries where it accounts for 13% of all the female cancers.[3]

Cervical cancer is rare in women under 30 years of age and most common in women over 40 years, with the greatest number of deaths usually occurring in women in their 50s and 60s,[4] with most women diagnosed in advanced stages.Cervical cancer results from genital infection with HPV (Human Papilloma Virus), which is a known human carcinogen.[5,6] A large multinational cervical cancer studies found that more than 90% of all cervical cancers worldwide are caused by eight HPV types: 16, 18, 31, 33, 35, 45, 52, and 58.[7]

Many prognostic factors have been recognized in patients with cancer cervix that affects treatment outcome and causes failure. These have been related to patient, tumorand treatment related factors. Patient related factors are - age, medical co-morbidities, renal status, blood haemoglobin level, HIV and HPV. Tumor related factors are - stage, lymph node involvement, parametrial extension, histology, grade and size of tumor. Treatment related factors are duration of treatment and total radiation dose and concurrent use ofchemotherapy.[8-11] So, the present study focuses to observe the outcomes of treatment and causes of failure in cervix cancer treated with concurrent chemoradiation based on the various prognostic factors.

MATERIALS AND METHODS

The study was conducted at Department of Radiation Oncology at R.R. Cancer Institute and Research Centre, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly.

Inclusive Criteria

Forty patients having provenbiopsy, age >18 years, Karnofsky performance scale above 70, stage IA to IIIB were chosen for the study also all patients haveno history of previous malignancy and hepatic, renal and cardiopulmonary functions were adequate.

Exclusion Criteria

Patients have carcinoma of the cervix FIGO stage IV, metastatic disease and any previous pelvic surgery, radiotherapy or chemotherapy were excluded from study.

Pre-treatment assessment was done by complete medical and physical examination including bimanual pelvic and rectal examination, cervical biopsy, baseline Haematological test (Hemogram, renal function test, liver function test), chest radiography, ultrasound Abdomen or CECT Abdomen and pelvis (whichever is feasible) and cystoscopy and proctosigmoidoscopy (only if clinically indicated).

All patients were planned and delivered by 3-DC radiotherapy using four field box technique. Radiotherapy dose delivered to pelvic area was 50 Gy in 25 fractions at 200 cGy/day. This was followed by intracavitary brachytherapy either 4 applications of 6 Gy/fraction or 3 applications of 7 Gy/fraction each as per departmental protocol. Total duration of the treatment was not more than 8 weeks.

Patients received cisplatin 35 mg/m2 weekly for a total of 5 cycles or 75 mg/m2 triweekly for a total of 2 cycles. Patients were adequately hydrated with 2 to 2.5 litres of fluids and supplemented with injectables KCL, MgSO4 and MVI. Radiotherapy was delivered within 1hr of administration of cisplatin and proper antiemetic therapy with 5-HT3 antagonist, dexamethasone, and ranitidine was given prior to chemotherapy administration.

Clinical response was assessed during radiotherapy and every month after radiotherapy for at least 6 months. The patients were assessed for objective tumour response according to WHO criterion includes complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

RESULTS

Present study evaluates prognostic factors in carcinoma of cervix. These have been divided into: patient related in terms of age and haemoglobin; tumor related in terms of stage, lymph node involvement, parametrial extension, histology, grade, hydronephrosis and size of tumorand treatment related factors in terms of duration of treatment and total radiation dose and concurrent use of chemotherapy.

Out of 40 patients, 60% (24/40) of patients was in the age group of less than 50 yrs. The youngest patient was 30 yrs old and oldest patient was 70 years. Twenty percent (8/40) of patients had hemoglobin level below 10 g/dl (Table 1).

Tumors related factors have been shown in Table 2. Grades were notreported in eight cases as slides and blocks were not available. Histological subtypes were not reported in 18 cases asslides and blocks were not available. Lymph node status and dimensions werebased on CT scan and ultrasound reports.

Treatment related factors have been enumerated in Table 3. Compliance for planned chemotherapy were observed in 31 patients (77.5%) and not observed in 9 patients (22.5%).

Table 1: Patient related factors

No. of Patients, n (%)	*Age*		*Haemoglobin*	
	≤50 yrs	>50 yrs	Below 10 g/dl	Above 10 g/dl
	24(60)	16(40)	8 (20)	32(60)

Table 2: Tumor related factors

Stage	*No. of Patients, n (%)*
Stage IB	0 (0)
Stage IIA	14 (35)
Stage IIB	17 (42.5)
Stage IIIA	2 (5)
Stage IIIB	7 (17.5)
Histological type	
Squamous cell carcinoma	38(95)
Adenocarcinoma	2(5)
Grades of differentiation	
Well Differentiated	14(35)
Moderately Differentiated	16(40)
Poorly Differentiated	2 (5)
No Comment	8(20)
Histological Subtype	
Non Keratinizing	6(15)
Keratinizing	16(40)
No Comment	18(45)
Lymph Node Status	
Positive Nodes	7 (17.5)
No Lymph nodes	33 (82.5)
Greatest Dimension	
<4 cm	15(37.5)
4-6 cm	14(35)
> 6cm	11(27.5)
Parametrial Extension	
Present	25(62.5)
Absent	15(37.5)

Table 3: Treatment related factors

Duration of treatment	*No. of Patients, n (%)*
≤ 8 weeks	33(82.5)
> 8 weeks	7(17.5)
Brachytherapy	
6×4	11(27.5)
7×3	29(72.5)
Compliance of planned chemotherapy	
Yes	31(77.5)
No	9(22.5)

Table 4: Age and haemoglobin Vs response at 6 Month

Age	*Total number of patients*	*No. of patients disease free at 6 months follow up, n (%)*	*p-value*
<50 yrs	24	19(79)	0.456
>50 yrs	16	11(69)	
Haemoglobin			
Below 10 g/dL	8	3(38)	0.006
Above 10 g/dL	32	27(84)	

The response corelation with age and haemoglobin is shown in Table 4. This difference in both the age groups for residual is statistically not significant (p = 0.456). Thedifference in haemoglobin level for residual disease is statistically significant (p = 0.006).

DISCUSSION

In cervical carcinoma in spite of best possible treatment a large number of cases present with local pelvic failure. Various attempts have been done to find out the prognostic factors in order to improve the survival by surgery alone, surgery combined with radiotherapy, radiotherapy alone, chemo radiotherapy, chemo radiotherapy plus targeted therapy. Present study evaluates prognostic factors in carcinoma of cervix which are subdivided into patient, tumor and treatment related factors.

Patient Related Prognostic Factors

Age

Age as a prognostic factor is controversial as Dattolli *et al*[12] showed a decreased survival in younger ages and in contrast Meanwell *et al,*[13] showed improved outcome for younger patients. In present study, 21% patients in age group < 50 yrs had residual within 6 months when compared to 31% residuals in women older than 50 yrs which was not statistically significant (p = 0.456). In elderly patients (above 70 years) poor survival is linked with incomplete treatment and presence of co-morbid conditions. The reason for poor survival in younger ages is correlated with more aggressive tumors such as adenocarcinoma and adenosquamous carcinomas. Poorly differentiated tumors are more frequent in younger ages. The other cause correlated is sexually transmitted exposure to aggressive strains of HPV.[14] However Mitchell *et al,*[15] evaluated 398 patients, divided patients into non elderly (35 to 69 yrs of age; n = 338) and elderly (≥ 70 yrs of age; n = 60) groups and stated that there was no significant difference in outcome in between two age groups.

Hemoglobin

In the study by Dunst *et al*[16] noted relapse rates were higher (67% versus 7%) if hemoglobin was <11 g/dL in comparison to the group having hemoglobin at least 13 g/dl. Haengsen *et al*[17] and Grinski *et al*[18] noted similar results. Lima and Bohlmann[19] found that pre-treatment Hb <12.0 g/dl was a negative factor for disease recurrence (HR 4.20, p = 0.031) and death (HR 8.19, p = 0.020). Anaemia is correlated with hypoxia, change in micro vessel of the tumor and leads to invasive phenotype of the tumor. Hypoxia is often associated with increased tumor glycolysis, angiogenesis and poor prognosis as well as invasion and metastasis by activating relevant gene expression through hypoxia inducible factor- 1 alpha (HIF- 1α).[20] The low hemoglobin had a marked impact on disease free survival (p = 0.006) in our present study as 62% had residual disease in patients who had hemoglobin less than 10 g/dl and 16% had residual disease in patients with hemoglobin above the level of 10 g/dL. Patients with low hemoglobin were given repeated transfusions. This appeared to be one of the strongest factors to impact on disease free survival. This study states the same as Dunst *et al*[16] and Grigiene[18] studies stated. In another study by Grigiene[21] of 162 patients with FIGO stage IIA-IIIB cervical carcinoma treated with irradiation, the Hb level before treatment showed significant influence on overall survival (p = 0.001), disease free survival (p = 0.040) and local control (p = 0.038). It has been recommended that blood transfusions are beneficial to anemic patients but should be given before start of radiotherapy to maximize its effect. Recombinant human erythropoietin (EPO) provides an alternative means of sustaining or raising hemoglobin levels during radiation therapy.

Tumor Related Prognostic Factors

Clinical Stage

The FIGO system has many shortcomings still FIGO stage is considered to correlate well with treatment outcome. Hacker *et al*[22] calculated the 5 yr overall survival according to different stages and reported 5-year survival of stage IB was 85%, IIA -77%, IIIA-IIIB- 43%, IVA-18%. Five year survival rates according to AJCC (2014) for stage IA- 93%, IB- 80%, IIA- 63%, IIB- 58%, IIIA- 35%, IIIB- 32%, IVA- 16% and IVB- 15% respectively have been reported. In India series published from Tata memorial hospital FIGO stage also has emerged as strong prognostic indicator (Shrivastava *et al*. 2014).[23]

Most patients with stage IIB tumors are treated with irradiation alone and 5 years survival rate is 60-65%.[24] Hanks *et al*[25] in a extended survey of pattern care studies noted the difference in 5 years survival in stage III carcinoma of cervix between the large centres with more facilities than with centres of less facility. The survival difference ranged from 69% to 28% respectively. Similarly over the years there is stage wise improvement with advancement of knowledge.

Attia *et al*[26] conducted a study in which a total of 83 patients records were analyzed. In multivariate analysis of this study, advanced stage was independent prognostic factor for poor OS (p = 0.001) and DFS (p = 0.003). Early stage comprises stage IB, IIA and IIB, and late stage comprises IIIA and IIIB.

In the present study of 40 patients 16% of patients in early stage group had residual within 6 months while 56% of patients in late stage had residual. These differences in various stages for residual are statistically significant (p = 0.016). So, present study also stating the same as above studies that stage is an important prognostic factor for DFS. Thus, lower is the stage better is the survival.

Histopathology, Grades and the Subtypes

While squamous cell carcinoma (SCC) is the predominant histology in cancer cervix, the second most common variety is the adenocarcinoma which makes up 8-20% of cancer cervix. Various studies have indicated lower response to therapy and poorer overall prognosis for adenocarcinoma, especially for non-early stages, i.e. locally advanced carcinoma.

According Tokumara *et al*[27] adenocarcinoma had 87% higher risk of failure than squamous cell carcinoma though no statistical significance was obtained. Increased incidence of lymph node involvement (31.6% versus 14.8%) and distant metastasis (37% versus 21%) in adenocarcinoma as compared to squamous cell carcinoma of similar stage and tumor diameter has also been reported.[28] In this study, the overall 5-year survival rates of stage Ib1 patients with ADC and SCC were 92.4% and 94.0%, respectively.

These are almost consistent with the 5-year survival rates of 88.7% for ADC and 89.1% for SCC[29] but a very large recent study by Konathala *et al*[30] demonstrated that keratinizing SCC may be less radiosensitive and associated with poorer survival in comparison to non-keratinizing SCC. Data showed that tumor histological grade (p < 0.001) and clinical stage (p < 0.001) were well correlated with cervical cancer recurrence after surgery. Patients with moderately and highly differentiated cancer of IB stage cancer were subject to lower recurrence rates when compared to patients with poorly differentiated cancer of IB stage cancer, respectively.[30]

In 2014, Nuranna *et al*[31] conducted a study which enrolled 447 cervical cancer patients and concluded that poor differentiation and other histopathology (neuroendocrine) had lower survival probability. Crissman *et al*[32] did not observe correlation between grade and survival. In an univariate analysis of Lee *et al*,[33] records of 61 patients were retrospectively reviewed, mixed tumor (101 vs. 34 months, p = 0.004) was shown to be poor prognostic factor. In a study by Hung in 2007, small cell carcinoma and adenocarcinomas were associated with poorer survival.[34]

In the present series of 40 patients studied, 38 the patients were squamous cell carcinomas. Out of these 38 patients, nine (24%) patients had residual. While in patients with adenocarcinoma histology residual was observed in one patient. This difference in histology for residual is statistically insignificant (p = 0.402). SCC was further classified as keratinizing and non- keratinizing subtypes. Of these subtypes, residuals were observed in 33% (2/6) of patients with nonkeratinizing and in 25% (4/16) of patients with keratinizing at end of 6 months after treatment. This difference in histological subtype for residual is statistically insignificant (p = 0.696). In our study, histological type and subtype are not influencing treatment outcome as these are insignificant factors. It is in contrast with the above studies and this is because of the involvement of other prognostic factors.

In this study, residual was observed in one patient with well differentiated grade. While in patients with moderately and poorly differentiated grade residual was observed in 39% (7/18) of patients at end of 6 months after treatment. This difference in grades of differentiation for residual is statistically significant (p = 0.039). It is in correlation with kumara and nuranna studies that states that higher grades have lower survival probability and poorer outcome.

Lymph Nodes

In a study by Endo in 2015, retrospectively reviewed records of 85 patients, pelvic lymph node enlargement, and distant metastasis were significantly and independently related to poor outcomes.[35] In a study of Park and Bae (2016),[36] medical records of 163 patients were retrospectively reviewed, the number of LN metastases was an independent risk factor for poorer survival outcomes in patients with cervical cancer (p = 0.021). In the present study lymph node positivity was observed in 17.5% (7/40). There was significant difference in the presence of residual disease (57% vs 18%, p = 0.031) in node positive and negative patients (57%) of the patients. Like other studies, in present study too lymph node involvement is a major risk factor for poorer survival outcomes in patients with cervical cancer.

Volume of Disease

Toita *et al*[37] reviewed of 70 patients with stage IIB and IIIB carcinoma of the uterine cervix treated with RT alone, reported no significant correlation of 5-year DFS with size of the cervical tumor<40 mm (70% to 85%); however, in patients with tumor>40 mm, the 5-year DFS was 28.6%. Delgado *et al*[38] found the 3 years disease free survival (DFS) to be 95 % for occult tumors, 86 % for those less than 3 cm and 68% for those greater than 3 cm (n = 732, p < 0.0001). Eifel *et al* (2009) also found similar results.[39]

In the present series, residual was observed in only one patient with volume of disease <4 cm (in greatest dimension). While in patients with volume of disease ≥4cm residual was observed in 36% of patients. This difference in volume of disease for residual is statistically significant (p = 0.038). Thus, it states that greater the tumor size poorer is the outcome. It is in correlation with the study done by Eifel *et al*[39] and Lee *et al*[33]. On the contrary, nuranna(2014) conducted a retrospective cohort study which enrolled 447 cervical cancer patients, stated that tumor size did not influence overall survival rate.

Parametrial Extension

Coia *et al*. (1990) reported a better 4 years survival rate (67% and 54%) and in-field tumor control rate (78% and 68%) in patients with unilateral versus bilateral parametrial involvement, respectively.[40] This study also compared the significance of unilateral/ bilateral parametrial involvement less or up to lateral pelvic wall. In a review of 1,178 patients with stage IIB disease treated at Washington University, the 5-year survival rates were 70% with medial parametrial and 58% with lateral parametrial involvement (p = 0.004).[25]

In the present study, residual was observed in 36% of patients with parametrial extension. While in patients without parametrial extension residual was observed in only one patient at end of 6 months after treatment. This difference in parametrial involvement for residual is statistically significant (p = 0.038). Our study results correlates with studies of coia*et al*, stating that parametrial involvement is a significant prognostic factor.

Hydronephrosis

International Federation of Gynaecology and Obstetrics (FIGO) recognizes obstructive nephropathy as a poor prognostic factor as FIGO-system upstages patients with disease not extending to the lateral pelvic wall to 'stage-IIIB' provided there is hydronephrosis which is not attributable to other causes. Pradhan *et al* conducted a study of 143 patients, 73 patients had no hydronephrosis (HN). Twenty nine patients (40%) with no hydronephrosis died compared to 61.5 % with unilateral hydronephrosis and 67% with bilateral hydronephrosis.[40] Hence, demonstrating that hydronephrosis is an independent poor prognostic indicator of survival in patients with advanced cervical cancer. Bilateral hydronephrosis compared to unilateral involvement confers a worse overall prognosis.

In our study, residual was observed in 75% of the patients with hydronephrosis while in patients without hydronephrosis residual was observed in 19% of patients. This difference in hydronephrosis for residual is statistically significant (p = 0.015). The study correlates with Pradhan *et al*, study, recognizing the hydronephrosis as a significant poor prognostic factor.[41]

Treatment Related prognostic factors

Duration of Treatment

Eifel *et al* (1999) concluded that better results are achievable when the treatment is completed in 8 weeks or less. Expected 1% decrement in local control for every additional day beyond 56 days.[42] Vishma *et al* conducted a study among the 380 cervical cancer patients and concluded that age at diagnosis, performance status at presentation, staging and treatment duration were the prognostic factors for cervical cancer.[43] In a study of Grigienė (2007) patients were analyzed, the radiotherapy duration had showed significant influence on overall survival (p = 0.045), disease free survival (p = 0.006) and local control (p = 0.033).[21]

In present study, residual was observed in 18% of the patients with treatment duration ≤8 weeks. While in patients with treatment duration >8 weeks residual was observed in 57% of the patients. This difference in duration of treatment for residual is statistically significant (p = 0.031). In correlation with Eifel *et al*[42] and Grigiene[21] study, our study concluded that prolonged duration of treatment is a significant prognostic factor that affects treatment outcome.

Total Radiation Dose

For acceptable local control total radiation dose at point A to be at least 85 to 90 Gy in 2 Gy/fraction equivalent.[44] To get better treatment outcomes, brachytherapy has to be integrated. In present study, all patients received >85Gy (EBRT + Brachytherapy) accept one patient. All patients received brachytherapy. Residual was observed in 27% of the patients who received 6Gy×4. While in patients who received 7Gy×3 residual was observed in 24% of the patients at end of 6 months after treatment. This difference in brachytherapy for residual is statistically insignificant (p value = 0.838).

Concurrent use of Chemotherapy

There seems to be survival benefit with CCRT over RT alone. Rose *et al*[45] summed the collective results of the

six North American randomized trials (including the NCIC study) and showed a cumulative and statistically significant 36% reduction in the risk of death favoring combined cisplatin-based chemoradiation over RT alone or combined with hydroxyurea. Furthermore, the NCI alert of 1999 which recommended the use of cisplatin CCRT was primarily based on five trials.[46] In a study by WuS (2013), 55 patients were analyzed, use of CCRT (p = 0.014) shows a good outcome, particularly in younger patients in an early FIGO stage.[47] A retrospective study by parveen (2006), concluded that outcome of treatment was improved when chemotherapy was added to radiation.[48] In our study, 31 patients showed compliance for planned chemotherapy. Poor compliance in 9 patients is because of poor nutritional support and reactions like nausea, vomiting and diarrhea etc. residual was observed in 26% of the patients with compliance of planned chemotherapy. While in patients without compliance residual was observed in 22% of the patients at end of 6 months after treatment. The correlation between chemotherapy compliance and residual disease is statistically insignificant (p = 0.827). More number of patients are to be recruited to validate it.

CONCULSION

Several significant prognostic factors are seen related to patient, tumor and treatment. The patient and tumor related factors cannot be controlled, but the clinician should be very careful about treatment related factors like overall treatment time. Further, presence of poor prognostic factors related to tumor may need intensification of the treatment by concurrent use of chemotherapy drugs, counteracting hypoxia by maintaining hemoglobin during treatment.

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